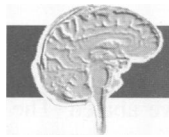



# Neurologic Effects of Alcoholism

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**Alcoholism, a worldwide disorder, is the cause of a variety of neurologic disorders. In this article we discuss the cellular pathophysiology of ethanol addiction and abuse as well as evidence supporting and refuting the role of inheritance in alcoholism. A genetic marker for alcoholism has not been identified, but neurophysiologic studies may be promising. Some neurologic disorders related to long-term alcoholism are due predominantly to inadequate nutrition (the thiamine deficiency that causes Wernicke's encephalopathy), but others appear to involve the neurotoxicity of ethanol on brain (alcohol withdrawal syndrome and dementia) and peripheral nerves (alcoholic neuropathy and myopathy).**

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Alcoholism is characterized by addiction to alcohol. Persons with this addiction crave alcoholic beverages and develop tolerance to its intoxicating effects. When they stop drinking, neurologic signs of withdrawal develop. This withdrawal syndrome is evidence of a physical dependence on ethanol. Alcohol abuse refers to recurrent episodes of excessive drinking despite serious economic, social, or medical consequences. Alcohol abuse does not usually produce physical dependence.[1]

Alcoholism is a worldwide disorder of enormous cost to society. In the United States more than 20% of hospital admissions involve medical complications of excessive drinking, and the annual socioeconomic cost of alcoholism is about $100 billion.[1] Persons with alcoholism have serious medical complications and commonly have alcoholic neurologic disorders. Most of these disorders, except Wernicke's disease, appear to be due to the neurotoxicity of ethanol.[2] Wernicke's encephalopathy is caused by thiamine deficiency, but genetic factors may play a role in affected patients. We review current concepts about the pathogenesis of alcoholism, alcoholic neurologic disorders, and genetic factors that may predispose persons to alcoholism and brain damage.

## Pharmacology

Ethanol enters the circulation within minutes of drinking and is quickly distributed throughout the body.[3] Virtually all alcohol is metabolized in the liver, where alcohol dehydrogenase converts ethanol to acetaldehyde, which, in turn, is metabolized by aldehyde dehydrogenase to acetate. An excessive accumulation of acetaldehyde causes an "alcohol-flush" reaction. This occurs in about 50% of Japanese and other Asians because they have a less active aldehyde dehydrogenase isoenzyme.[4] Affected persons experience hot sensations associated with vasodilatation and facial flushing, tachycardia, and hypotension. Possibly because of these unpleasant experiences, Japanese people with reduced aldehyde dehydrogenase activity have a lower rate of alcoholism.[4]

Disulfiram (Antabuse) inhibits aldehyde dehydrogenase and has been used prophylactically to discourage drinking in patients with alcoholism.[5] If treated patients drink alcohol, they have a more severe "acetaldehyde syndrome," characterized by intense palpitations, throbbing headache, nausea and vomiting, weakness, and vertigo. Disulfiram use discourages drinking but does not cure alcoholism.[6]

### *Intoxication*

Ethanol readily crosses the blood-brain barrier, and consequently, brain and blood alcohol concentrations equilibrate rapidly after drinking. Intoxication develops in nonalcoholic persons at blood alcohol levels of 10 to 35 mmol per liter (50 to 150 mg per dl) and is more severe when blood levels are rising.[3] There is usually euphoria, a loss of social inhibitions, and garrulous behavior, but sometimes intoxicated people are gloomy and belligerent. Some do not experience euphoria but only become drowsy; they rarely abuse alcohol. At higher blood ethanol concentrations, cerebellar and vestibular function deteriorates, and lethargy and stupor may supervene. In nonalcoholic persons, blood ethanol concentrations of

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**ABBREVIATIONS USED IN TEXT**

cyclic AMP = adenosine 3′:5′-cyclic phosphate
GABA = γ-aminobutyric acid
$5\text{-HT}_3$ = 5-hydroxytryptamine$_3$
LS = long sleep [mouse line]
MAO = monoamine oxidase
MRI = magnetic resonance imaging
NMDA = *N*-methyl-D-aspartate
SS = short sleep [mouse line]

110 mmol per liter (500 mg per dl) can be fatal, usually because of respiratory depression and hypotension. Persons with alcoholism are more resistant to ethanol intoxication than nonalcoholic persons.[7-10]

Alcoholic "blackouts" can occur during heavy drinking and are characterized by hours of amnesia while awake. Immediate recall and long-term memory are normal, but new events are forgotten, as in patients with transient global amnesia. Although alcoholic blackouts have been related to reduced plasma tryptophan levels,[11] ethanol inhibition of *N*-methyl-D-aspartate (NMDA) receptor-stimulated calcium flux in the hippocampus may be more important.[12-15]

*Tolerance*

Tolerance to alcohol can be acute or chronic. "Acute tolerance" to alcohol develops rapidly[3,16]; after drinking several hours, a person can appear to be sober at blood alcohol levels that caused intoxication earlier.[17] "Chronic tolerance" is a characteristic feature of alcoholism, and alcoholic persons can appear sober at blood alcohol concentrations of 90 to 110 mmol per liter (400 to 500 mg per dl).[9] The highest recorded level is 330 mmol per liter (1,510 mg per dl) in an ambulatory person with chronic alcoholism who had stopped drinking three days earlier.[8] Tolerance is caused by adaptive molecular changes in the brain.

*Alcohol Withdrawal Syndrome*

When drinking is abruptly reduced or discontinued, a hyperexcitable withdrawal syndrome develops that is considered to be evidence of "physical dependence."[18] Clinical features include tremulousness, disordered perceptions, convulsions, and delirium tremens.[16] These symptoms and signs appear to be due to adaptive neural mechanisms that are no longer opposed by the depressant effects of ethanol.

Tremor is a common symptom, beginning six to eight hours after the last drink and worsening in one to two days. Sympathetic hyperactivity with elevated levels of norepinephrine and its metabolites has been documented,[19] and treatment with sympatholytic drugs can be helpful.[20,21] The calming effects of benzodiazepines, however, are more effective.

Disordered perceptions may parallel the development of tremor and sympathetic hyperactivity, becoming most pronounced at 24 to 36 hours and clearing in a few days. Ordinary visual, auditory, and sensory experiences become distorted and misinterpreted. Vivid nightmares interfere with sleep. Auditory hallucinations ("alcoholic hallucinosis") can persist for weeks, even though other manifestations of ethanol withdrawal have abated. The goal of treatment with benzodiazepines is to suppress symptoms and produce mild sedation.

Generalized tonic-clonic convulsions can develop within one to two days after reducing or stopping drinking.[16] Multiple seizures are common and usually occur over 6 to 12 hours; status epilepticus is unusual. Some attribute the development of seizures to ethanol intoxication, not withdrawal.[22] But ethanol dependence is followed by withdrawal seizures in animals, and mice have been bred in the laboratory to have convulsions on ethanol withdrawal.[23] Phenytoin is not useful in managing alcohol withdrawal seizures,[24] but sedating doses of benzodiazepines are effective.[25] Calcium channel antagonists may prove to be beneficial,[26,27] but further study is needed.

Agitation, global confusion, insomnia, frightening hallucinations, and sympathetic hyperactivity characterize delirium tremens. These alarming manifestations develop abruptly several days after the occurrence of tremors and generalized hyperexcitability. This is a serious disorder, and associated electrolyte abnormalities, hyperthermia, and dehydration with circulatory collapse can be fatal. Therapy includes fluid replacement, the correction of associated electrolyte disorders such as hypokalemia and hypomagnesemia, and sedation with benzodiazepines.

## Cellular Pathophysiology of Ethanol Intoxication, Tolerance, and Physical Dependence

Acute and chronic ethanol-induced changes in membrane-dependent events appear to be related to acute intoxication, tolerance, and physical dependence. Ethanol intercalates into cell membranes,[28] increasing membrane fluidity,[29] but it is not clear how changes in membrane order control physiologic function.[30] Recent evidence suggests that proteins involved in signal transduction may be more important pathophysiologic targets for alcohol. Components of signal transduction cascades that adapt to ethanol include ion channels,[31-34] second messengers,[35-39] neurotransmitters and their receptors,[15,40-43] G proteins,[44-46] chaperonins,[47] and regulators of gene expression.[47,48]

*γ-Aminobutyric Acid Receptors*

γ-Aminobutyric acid (GABA) is the predominant inhibitory neurotransmitter in the brain. Two types of GABA receptors have been described, $\text{GABA}_\text{A}$ and $\text{GABA}_\text{B}$. $\text{GABA}_\text{A}$ receptors are hetero-oligomeric protein complexes that contain a chloride ionophore and have specific allosteric binding sites for benzodiazepines and barbiturates.[49] Intoxicating concentrations of ethanol (5 to 50 mmol per liter [22 to 220 mg per dl]) increase chloride flux through $\text{GABA}_\text{A}$-receptor-operated chloride channels, and this effect is blocked by the GABA antagonists, bicuculline and picrotoxin.[41,50]

Selected lines of mice and rats have been used to detect genetic differences in $\text{GABA}_\text{A}$ receptors that may contribute to differences in behavioral responses to

ethanol. The "long-sleep" (LS) and "short-sleep" (SS) mouse lines were selected for differential sensitivity to the hypnotic effect of ethanol.[51] Chloride 36-flux in membrane vesicles made from LS mice is more sensitive to enhancement by ethanol and benzodiazepines than in vesicles from SS mice. Similar results have been found in other rodent lines, all suggesting a strong association between in vivo ethanol intoxication and in vitro inhibition of chloride flux by ethanol. These differences in $GABA_A$-activated chloride channel function are maintained when $GABA_A$ receptors are expressed in *Xenopus laevis* oocytes using messenger RNA from brains of LS and SS mice.[52] The biochemical basis for these differences in $GABA_A$ receptors from LS and SS mice is not yet known.

Several genes encoding subunits for the $GABA_A$-receptor complex have now been cloned. At least six different α clones, three β sequences, two γ subtypes, and one δ clone have been described.[49,53,54] The γ2 subunit exists as alternatively spliced short (γ2s) and long (γ2l) forms, the latter containing 24 additional nucleotides that encode a phosphorylation site for protein kinase C on an intracellular loop.[55] Recent evidence from studies of messenger RNA expression in *X laevis* oocytes indicates that the γ2l subunit is required for ethanol potentiation of $GABA_A$-receptor activation.[56]

Benzodiazepine inverse agonists, such as the imidazobenzodiazepine Ro15-4513, prevent the intoxicating, antianxiety, and anticonvulsant effects of ethanol in rodents and antagonize ethanol enhancement of agonist-stimulated chloride flux through $GABA_A$ receptors.[41,50,57,58] Thus, it may be possible to design safe drugs that modulate $GABA_A$-receptor function to block the acute intoxicating effects of ethanol in humans.

### *Calcium Channels*

Ethanol-induced changes in calcium channels may account for some of the signs and symptoms of ethanol withdrawal. Exposure to ethanol for several days increases depolarization-stimulated calcium chloride Ca 45 uptake.[33,59] Calcium flux remains elevated for several hours after the removal of ethanol[33,59] and is associated with an increase in the number of binding sites for dihydropyridine calcium channel antagonists.[33,59,60] Increases in dihydropyridine-sensitive calcium channels could induce withdrawal symptoms by promoting neurotransmitter release.[61] The importance of calcium channels in the pathogenesis of alcohol withdrawal syndromes is supported by evidence that calcium channel antagonists reduce the incidence of tremors, seizures, and death in alcohol-dependent mice and rats deprived of ethanol[27,62] and reduce withdrawal symptoms in patients with alcoholism.[26] Ethanol-induced stimulation of dihydropyridine binding sites is much greater in mice selectively bred for severe alcohol withdrawal seizures than in mice bred for mild signs of alcohol withdrawal.[63] Therefore, the magnitude of alcohol withdrawal may be regulated by genetic factors that control the expression of dihydropyridine-sensitive calcium channels.

### *Excitatory Amino Acids*

In the nervous system, glutamate, aspartate, and their structural analogues bind to receptors that regulate ion channels or activate phosphoinositide hydrolysis.[64] Specific receptors respond to the excitatory amino acid agonists, NMDA, kainate, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, or L-2-amino-4-phosphonobutanoic acid, but the NMDA receptor is particularly sensitive to ethanol. Intoxicating concentrations of ethanol (5 to 50 mmol per liter) inhibit NMDA-activated calcium currents in rat hippocampal neurons[13] and dorsal root sensory neurons[15] and reduce NMDA-stimulated calcium uptake in cerebellar granule cells.[12] Intoxicating concentrations of ethanol also inhibit cellular responses to NMDA-receptor activation, including neurotransmitter release,[65] cyclic guanosine monophosphate production,[12] and the generation of excitatory postsynaptic potentials.[14] *N*-Methyl-D-aspartate receptors are important for long-term synaptic potentiation, which appears to play an important role in learning and memory.[66] Thus, ethanol inhibition of NMDA receptors may explain cognitive defects and "blackouts" associated with intoxication and binge drinking.[12]

Long-term exposure to ethanol causes an increased expression of glutamate receptors in the brains of alcoholic humans and synaptosomes from rats administered ethanol for two to three weeks.[67,68] Recent evidence suggests that the increases also contribute to the generation of alcohol-withdrawal seizures.[69]

### *Dopamine and Serotonin*

Dopamine is implicated in neural mechanisms of reward, reinforcement, and craving, and psychoactive drugs, including ethanol, increase dopamine release from mesolimbic regions in rats.[70] 5-Hydroxytryptamine$_3$ (5-$HT_3$) receptors control dopamine release,[71] and in mesolimbic regions, dopamine release induced by ethanol is blocked by 5-$HT_3$ antagonists.[72,73] Ethanol potentiates 5-$HT_3$-receptor activation,[74] and 5-$HT_3$-receptor antagonists reduce ethanol intake[75] and the ability to discriminate between water and alcohol. These findings suggest that serotonin, acting at 5-$HT_3$ receptors, may mediate some aspects of ethanol intoxication and ethanol-seeking behavior.

### *Adenosine Transporters, $A_2$ Receptors, and Adenosine 3′:5′-Cyclic Phosphate Production*

Adenosine is an inhibitory neuromodulator in the nervous system. Adenosine modulates calcium channels, the release of neurotransmitters, and the activation of neurotransmitter receptors.[76,77] Recent evidence suggests that adenosine may mediate many of the effects of ethanol in the brain.[42,78-81] Acute ethanol exposure inhibits adenosine uptake by a specific kind of nucleoside transporter.[82] This causes an accumulation of extracellular adenosine,[79,80] which activates adenosine $A_2$ receptors, thereby increasing the levels of adenosine 3′:5′-cyclic phosphate (cyclic AMP).[35,36,83] With prolonged ethanol exposure, increases in cyclic AMP are usually followed by adaptive desensitization of cyclic-AMP production.[36] This appears to be a "heterologous desensitization" of receptors coupled posi-

tively to adenylyl cyclase by the stimulatory G protein, $G_S$.[45] Such cells require ethanol to maintain normal levels of cyclic AMP,[36] and thus they represent an example of physical dependence on ethanol at a cellular level. Ethanol-induced heterologous desensitization appears to be due primarily to a decrease in messenger RNA for $G\alpha_S$,[45] the guanosine triphosphate-binding component of $G_S$. This causes a reduction in $G\alpha_S$ protein[44,45] and decreases functional coupling between receptors and adenylyl cyclase.[45] Under these conditions, the adenosine transporter loses its sensitivity to ethanol inhibition, presumably because of reduced cyclic AMP-dependent protein kinase A activity. Thus, in naive cells, adenosine uptake is inhibited by acute ethanol exposure, but uptake becomes insensitive to ethanol inhibition after long-term ethanol exposure.[80] This is an example of "chronic tolerance" to ethanol at a cellular level.

The pathophysiologic importance of altered adenosine regulation and desensitization of cyclic AMP production is suggested in studies of circulating lymphocytes from actively drinking alcoholic persons. Cells from patients with alcoholism show a striking reduction in cyclic-AMP levels and a desensitization of adenosine-stimulated cyclic-AMP production.[35] In addition, nucleoside transport appears to be altered in actively drinking alcoholic persons as their blood cells are resistant to the inhibition of adenosine uptake by ethanol (discussed later). It may be anticipated that adenosine receptor antagonists acting at specific sites in the brain could prevent many of the acute and chronic effects of ethanol on cyclic-AMP signal transduction and, perhaps, prevent acute intoxication and physical dependence.

## Genetic Studies of Alcoholism

Considerable evidence exists that genetic factors play a role in alcoholism. Alcoholism is about seven times more frequent in first-degree relatives of alcoholic persons than in the general population.[84] In addition, 16% to 26% of fathers and 2% to 6% of mothers of alcoholic persons also have alcoholism.[84] Identical twins have a significantly higher concordance of alcoholism than fraternal twins, even when environmental factors, such as the greater frequency of social contact between identical twins, are taken into account.[85,86] The strongest evidence for heritability of alcoholism has come from adoption studies. Among alcoholic patients with severe alcohol-related behavioral or medical complications, adoptees have an average of 2.5 times greater chance of alcoholism developing if at least one biologic parent had alcoholism.[84]

Based on the results of Swedish adoption studies, Cloninger described two subtypes of alcoholism.[87] Type 1 is more common among men and women with female alcoholic relatives, whereas the type 2 syndrome is characteristic of male relatives of alcoholic men. Those with type 1 alcoholism tend to drink excessively later in life, usually after an extended period of social drinking. They can abstain from alcohol or engage in binge drinking. Associated personality traits in type 1 alcoholism include anxiety, high reward dependence, emotional dependence, rigidity, and perfectionism. Type 2 alcoholism is associated with antisocial personality traits such as impulsivity, fighting, drunk driving, and criminal behavior. Persons with type 2 alcoholism begin drinking in their teens or early adulthood, actively seek alcohol, and usually cannot abstain from drinking. Whether this classification scheme will prove to be useful in clinical and genetic studies remains to be determined.[88]

### *Linkage Analysis of Alcoholism*

Studies linking alcoholism with the chromosome 4q blood group marker MNS and the esterase D marker on chromosome 13q have been reported,[89,90] but these results are inconclusive for substantial linkage. Recently a complementary DNA probe, which contains the last coding exon of the dopamine $D_2$-receptor gene and 16.5 kilobases of the noncoding sequence on chromosome 11, has been used to examine brain tissue from 35 persons with and 35 without alcoholism.[91] These results provided statistical evidence for the presence of a genetic locus of susceptibility to a severe form of alcoholism in the q22-q23 region of chromosome 11. Several authors have criticized the criteria used for retrospectively diagnosing alcoholism in this study and have warned against overinterpreting the results from such a limited number of patients.[92-94] Moreover, a subsequent study of 40 living, unrelated persons with alcoholism and two families with multigenerational alcoholism failed to confirm this linkage.[95] Clearly, much work is necessary to identify the gene(s) involved in alcoholism. This is likely to be a formidable problem because the contribution of a specific genotype will be complicated by the heterogeneity of alcoholism and the absence of precise diagnostic criteria. For example, in families with a history of alcoholism, some individuals with genetic risk might choose never to drink, while others without genetic risk might become alcoholic because of socioeconomic reasons. Therefore, even if a probe for a linked gene were used in linkage studies in families, it might not be possible to achieve a significant lod score because of the heterogeneity of alcoholism. Multigenic approaches may prove to be more valuable. Also, it may be more plausible to search for phenotypic biochemical or molecular markers of alcoholism. Once a candidate phenotype is recognized, it should be possible to identify specific genes involved in alcoholism.

## Possible Phenotypic Markers of Genetic Alcoholism

### *Behavioral and Neurophysiologic Markers*

Subjective and objective measurements of intoxication can be correlated with blood alcohol concentrations so that the sensitivity of neurologic responses to alcohol can be studied for a genetic linkage to alcoholism.[96] In studies of subjects whose parents had alcoholism, a reduced sensitivity to ethanol is suggested, but a definitive genetic marker has not been identified. Neurophysiologic studies may be more promising. Changes in electroencephalographic activity and sensory-evoked responses have been reported in the offspring of alcoholic persons,

and the amplitude of the P300 component of event-related brain potentials may be reduced in young sons of persons with alcoholism.[97,98]

*Biochemical Markers*

Numerous studies have documented decreased levels of platelet monoamine oxidase (MAO) activity in alcoholic persons.[99] Low MAO activity may be more common in alcoholic persons and those who abuse mixed drugs who have personality traits consistent with type 2 alcoholism.[100,101] There is much overlap between individual patients and controls, however, and MAO activity in alcoholic patients fluctuates with abstinence, suggesting that decreases in MAO activity result from alcohol exposure. Ethanol inhibits platelet MAO activity, and inhibition is greater in platelets from alcoholic subjects than from controls.[102] This difference does not appear to be associated with the duration of abstinence from alcohol, suggesting that ethanol inhibition of MAO activity may involve inherited factors.

Freshly isolated lymphocytes from alcoholic persons who drink heavily show a 76% reduction in basal and receptor-stimulated cyclic-AMP levels when compared with age- and sex-matched controls and patients with nonalcoholic liver disease.[35] Subsequent studies in platelet membranes from alcoholic patients have also shown a reduction in prostaglandin $E_1$-stimulated cyclic-AMP levels.[102] Freshly isolated lymphocytes from heavily drinking patients with alcoholism show a desensitization of adenosine receptor-dependent cyclic-AMP production[83] that mimics changes produced by adding ethanol to neural cells in culture.[36,45] When lymphocytes from alcoholic subjects and controls were cultured for seven to eight days in the absence of ethanol, the cells from alcoholic persons recovered and basal cyclic-AMP levels were the same as controls. When these same lymphocytes were administered adenosine, they showed a 2.8-fold greater stimulation of cyclic-AMP production than did lymphocytes from nonalcoholic subjects.[83] In addition, lymphocytes from alcoholic subjects were more sensitive to ethanol than cells from nonalcoholic subjects. After ethanol treatment for 24 hours, lymphocytes from alcoholic subjects exhibited desensitization of cyclic-AMP signal transduction, whereas cells from nonalcoholic persons showed no change under the same conditions.[83] Because these differences were observed after four to six cell divisions in the absence of ethanol, they may reflect genetic differences between alcoholic and nonalcoholic subjects.

Freshly isolated lymphocytes from alcoholic subjects also exhibit abnormal lipid metabolism. Ethanol is an exogenous substrate for phospholipase D, leading to the accumulation of phosphatidylethanol.[103-105] Lymphocytes from alcoholic patients show increased synthesis of phosphatidylethanol[105]; it is not known whether this is due to genetic factors or to continued exposure to ethanol.

## Alcohol-Related Neurologic Disorders

With prolonged drinking, there is a curious transition between reversible metabolic effects of ethanol and the development of organ damage in the brain and elsewhere. Some propose that malnutrition is the cause of most alcohol-related neurologic disorders.[106] People with alcoholism often obtain as much as 50% of their calories from ethanol, and serious nutritional deficiencies can develop, particularly for protein, thiamine, folate, and niacin. On the other hand, studies of well-nourished alcoholic patients with skeletal and cardiac alcoholic myopathy suggest that a lifetime threshold of ethanol consumption is exceeded before irreversible muscle damage occurs.[107] In addition, recent evidence suggests that genetic factors contribute to the diverse toxicity of ethanol.[108] Ethanol can also be an exogenous substrate for specific enzymes leading to the accumulation of possibly toxic abnormal products. These include phosphatidylethanol[103-105] and fatty-acid ethyl esters.[109,110] In addition, acetaldehyde is a possible toxin. Acetaldehyde can react with diverse proteins to form acetaldehyde-protein adducts that accumulate in proportion to the amount of ethanol consumed during chronic alcoholism.[111,112] Prolonged ethanol-induced changes in receptor-stimulated second messenger production and ion-channel function could also be cytotoxic, particularly for organs with little cell turnover, such as brain, muscle, and liver.

*Wernicke's Encephalopathy and Korsakoff's Psychosis*

Wernicke's encephalopathy is caused by thiamine deficiency[113,114] and is characterized by the triad of ataxia, oculomotor abnormalities, and global confusion. On microscopic examination, demyelination, necrosis, gliosis, and vascular proliferation occur in the mamillary bodies, superior cerebellar vermis, hypothalamic nuclei, and other gray matter regions of the diencephalon and brain stem. Most patients have chronic alcoholism, but cases associated with persistent vomiting, starvation, renal dialysis, iatrogenic malnutrition, and malignant neoplasms have also been reported. Therefore, Wernicke's encephalopathy should be suspected in any poorly nourished patient with altered mental status.

Because cerebellar lesions are most severe in the superior vermis, patients usually have gait ataxia with few signs of limb incoordination. Nystagmus is the most common ocular sign. Bilateral rectus palsies and horizontal conjugate defects are also common. Vertical gaze palsies occur less frequently, and complete ophthalmoplegia is rare. Other infrequent findings include ptosis, internuclear ophthalmoplegia, and loss of pupillary reflexes.

The acute confusional state is characterized by inattention, disorientation, and sleepiness. Sometimes patients are agitated, but most are apathetic, indifferent, and amnestic. Impaired consciousness can be an important feature in otherwise unrecognized cases of Wernicke's encephalopathy, so that this diagnosis must be considered in all patients with unexplained stupor and coma. In addition to the classic triad, patients may have hypotension or hypothermia due to hypothalamic involvement. Most patients have associated polyneuropathy (discussed later).

In alcoholic patients, thiamine deficiency may result from an inadequate diet, impaired intestinal absorption, and decreased hepatic thiamine storage.[115] Four enzymes involved in intermediary metabolism require thiamine pyrophosphate as a cofactor: pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, transketolase, and branched-chain α-ketoacid dehydrogenase. The affinity of transketolase for thiamine is reduced in some patients with Wernicke's encephalopathy.[116,117] These patients are at greater risk for functional thiamine deficiency to develop when thiamine levels in the diet are marginal.

Autopsy studies indicate that Wernicke's encephalopathy is much more prevalent than recognized during life. Although the diagnosis is usually made on clinical grounds, computed tomography and magnetic resonance imaging (MRI) may aid in diagnosing mild or atypical cases.[118,119] The volume of the mamillary bodies is reduced in chronic Wernicke's encephalopathy. Calculating the volume of the mamillary bodies by MRI can distinguish patients with Wernicke's encephalopathy from unaffected controls or patients with Alzheimer's disease.[118]

If the disease is untreated, the mortality rate is 10% to 20%. Diagnosis is critical because treatment usually corrects most or all of the abnormalities. Because patients are at risk for cardiovascular collapse, Wernicke's encephalopathy must be considered a medical emergency. Patients should be admitted to a hospital and thiamine, 100 mg per day for several days, administered parenterally to ensure absorption. It is important to begin therapy before feeding or administering parenteral glucose solutions because carbohydrates can precipitate or worsen the encephalopathy. Outpatient therapy should continue with at least 50 mg of thiamine per day because thiamine absorption is often impaired in patients with alcoholism. With treatment, ocular abnormalities may resolve within hours to a few days; confusion and ataxia usually resolve more slowly.

Sequelae include gait ataxia, nystagmus, and Korsakoff's psychosis. Korsakoff's psychosis is a chronic amnestic disorder that occurs in most patients who survive Wernicke's encephalopathy.[114,120] Remote memories remain intact, but there is retrograde amnesia for recent memories, and patients are usually disoriented to place and time. Particularly striking is an inability to learn new information (anterograde amnesia). Immediate recall is intact, but patients are unable to remember the same information several minutes later. They appear to be unaware of their deficit, and confabulation is common. Alertness and other aspects of cognitive function are unaffected. Lesions in the dorsal medial nuclei of the thalamus are probably responsible for the memory deficits.[121] About 25% of patients never recover and require long-term care, whereas 20% recover completely over several months.[113] It is not clear whether thiamine is effective in treating Korsakoff's syndrome.

*Alcoholic Cerebellar Degeneration*

A cerebellar syndrome occurs in some patients with alcoholism. It is characterized by gait ataxia with lesser degrees of limb ataxia affecting the legs more than the arms.[114] The syndrome occurs after several years of alcoholism and usually develops gradually. There is loss of cerebellar cortical neurons, particularly in the anterior and superior vermis, and less often in the anterior and superior cerebellar hemispheres. Because this is similar to cerebellar lesions seen in Wernicke's encephalopathy, some clinicians attribute alcoholic cerebellar degeneration to thiamine depletion. The disorder may also result from a direct toxic effect of alcohol or from electrolyte derangement.[122] The development of cerebellar degeneration does not correlate with the amount of alcohol consumed,[123] and affected patients appear to drink less than other alcoholic persons. This suggests that cerebellar damage may develop in some alcoholic persons because of genetic vulnerability. Cerebellar dysfunction frequently abates or stabilizes with abstinence and improved nutrition.[124]

*Alcoholic Dementia*

Cognitive deficits attributed to a neurotoxic effect of ethanol frequently develop in persons with alcoholism; this observation is supported by experimental and histologic data. Several studies have provided evidence for a direct neurotoxic effect of ethanol on the brain. In rodents, long-term ethanol consumption causes learning deficits, altered dendritic structure, and a loss of neurons.[125] Courville first described neuropathologic changes in alcoholic persons with dementia, including cortical atrophy, enlargement of the lateral ventricles, and a loss of cortical neurons.[126] Lynch examined the brains of 11 persons with alcoholism and described a patchy loss of cortical neurons.[127] In quantitative autopsy studies, a statistically significant loss of brain tissue and a loss of cortical neurons were found, especially in frontal cortex, in alcoholic patients.[128,129] Some authors have argued that such findings are nonspecific or artifactual and that unrecognized Korsakoff's syndrome accounts for most cases of mental impairment among alcoholic persons.[114,130]

Computed tomographic and MRI studies have shown symmetrical enlargement of lateral ventricles, increased size of cerebral sulci, and increases in the width of interhemispheric and sylvian fissures in alcoholic patients. In addition, patients with alcoholism commonly have cognitive deficits on psychometric tests. Radiographic changes and psychological test performance may improve if drinking is discontinued, suggesting that cerebral atrophy and cognitive deficits are partially reversible.[131] Reversible atrophy may be due to alterations in dendritic structure that are reversed by abstinence in rats with long-term exposure to ethanol.[132] Other disorders that cause impaired cognitive function in persons with alcoholism include thiamine deficiency, pellagra, hepatocerebral degeneration, recurrent head trauma, and Marchiafava-Bignami disease.

*Central Pontine Myelinolysis*

Central pontine myelinolysis is an uncommon disorder found most often in alcoholic patients. Hyponatremia frequently precedes this disorder, and aggressive correc-

tion of chronic hyponatremia appears to be the major precipitating factor in humans and animals.[2] Characteristically, there is bilaterally symmetrical, focal destruction of white matter in the ventral pons, and about 10% of patients have extrapontine lesions in the thalamus, basal ganglia, cerebellum, and cerebral white matter. The lesions exhibit a loss of myelin and a reduced number of oligodendroglia, with relative sparing of neurons and axons and no inflammation or vascular changes.

Typically central pontine myelinolysis evolves over days to weeks. Mental confusion is prominent. Demyelination of pontine corticobulbar fibers may lead to dysarthria, mutism, dysphagia, facial and neck weakness, conjugate gaze palsies, and impaired tongue movement. Corticospinal tract lesions in the pons produce paraparesis or quadriparesis. In severe cases a "locked-in" syndrome may develop.

The cerebrospinal fluid is normal or may show elevated pressure and increases in protein, including myelin basic protein. Brain-stem auditory evoked potentials may be abnormal and improve as the patient recovers. Magnetic resonance imaging is more sensitive than computed tomography for detecting pontine lesions.[133] Patients with central pontine myelinolysis should be supported vigorously because they can improve after several weeks.[134]

*Alcoholic Neuropathy*

Polyneuropathy is the most common neurologic complication in alcoholism. Patients report paresthesias, pain, and weakness, especially in the feet. Dysesthesias can be so severe that they interfere with walking. Examination reveals reduced pain and temperature sensation. Distal muscle weakness and atrophy are common, greater in the legs than in the arms. Deep tendon reflexes are reduced, and ankle reflexes are usually absent, even in asymptomatic patients. Cerebrospinal fluid protein levels are usually normal or slightly elevated.

Alcoholic polyneuropathy is characterized by axonal degeneration and demyelination. Although earlier clinical evidence suggested that inadequate nutrition was responsible,[106] a specific vitamin deficiency has never been documented. Recent evidence suggests a direct neurotoxic effect of ethanol on peripheral nerves.[135,136] Alcoholic persons frequently suffer entrapment or pressure neuropathies, particularly of ulnar and peroneal nerves.[137] Recovery in abstinent patients is slow and often incomplete, requiring weeks to months.

*Alcoholic Myopathy*

Acute alcoholic myopathy is a dramatic and life-threatening disorder that can develop after several days of heavy binge drinking.[138] Patients experience pain, cramps, tenderness, proximal weakness, and swelling of the muscles, sometimes associated with cardiac arrhythmias. Blood creatine kinase levels are elevated, associated with rhabdomyolysis and myoglobinuria. This frequent complication may lead to hyperkalemia, renal failure, and death. Recovery usually occurs within days to weeks of abstinence, but residual weakness in proximal muscles may remain.

Chronic alcoholic myopathy is usually a painless syndrome of proximal muscle weakness and atrophy that is not often recognized. Nearly 50% of asymptomatic persons with alcoholism probably have a skeletal myopathy.[107] Myopathy can be mild or severe, and coexistent alcoholic peripheral neuropathy may contribute to the weakness. Alcoholic skeletal myopathy and alcoholic cardiomyopathy have been reported to develop simultaneously in well-nourished alcoholic persons, and there is a direct relationship between the amount of ethanol consumed and the severity of the myopathies.[107] Improvement usually occurs two to three months after discontinuing drinking. Repeated ethanol administration to human volunteers for 28 days causes muscle damage despite adequate nutrition, indicating that myopathy results from ethanol toxicity and not nutritional factors.[139] Current concepts suggest that myopathy is due to direct toxicity of ethanol, acetaldehyde, or other ethanol metabolites.[107,138]

## Summary

Research on alcoholism is ready to benefit from major advances in molecular genetics and cell biology that are fueling a revolution in the diagnosis and treatment of disease. Alcohol-induced changes in gene expression and signal transduction probably mediate alcohol tolerance, dependence, and neurotoxicity. In addition, inherited factors appear to regulate drug-seeking behavior, the development of tolerance to alcohol, and susceptibility to the neurotoxic effects of alcohol. The discovery of genes that confer risk for alcoholism and alcohol toxicity, and understanding fundamental alcohol-induced changes in gene expression and cellular function, will make it possible to design new therapies to prevent or ameliorate alcoholism and alcoholic neurologic disorders.

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